HerediGENE

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Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :	**Date Received :**
Medical ID :	**Date of Report :**
Date of Birth :	**Req. Physician :**
Location :	**Barcode :**
Material :	**Sample acceptability :**

HerediGENE: ***Hereditary Cancer Panel by Next Generation Sequencing***

Result

NEGATIVE

NO PATHOGENIC VARIANT IDENTIFIED

Interpretation

This result reduces the likelihood of hereditary predisposition to cancer. However, some variants in genes of this panel may not be detected by the used methodology. Genes not included in this panel, may also contribute to increased cancer risk. Molecular genetic testing result should always be co-evaluated with the clinical symptoms and family history of the patient.

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Methodology

Genomic DNA was extracted from the sample under investigation and was analysed by Next Generation Sequencing (NGS) using a target enrichment panel containing 83 genes involved in hereditary predisposition to cancer (Common Hereditary Cancer NGS Panel, CliSeq, G2M) (see table). Among them, 17 genes are involved in the homologous recombination (HR) complex. Sequencing was carried out using MGI technology. Reads were aligned to the reference sequence (GRCh37), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript.

The presence of genetic variants was investigated using the commercial computational algorithm SeqPilot (JSI Medical System). All clinically significant variations were confirmed by Sanger Sequencing. All targeted regions within exons were sequenced with ≥20x depth. This assay targets all coding regions of the indicated transcripts, 20 base pairs of flanking intronic sequences and 25 base pairs of flanking intronic sequences for *BRCA1* and *BRCA2* genes. In addition, the computational algorithm panelcn.MOPS (PMID: 28449315) was also used to detect large genomic rearrangements (LGRs) in the *BRCA1* and *BRCA2* genes. The presence of LGRs is verified by use the MLPA method (Multiplex Ligation-dependent Probe Amplification, MRC Holland; PMID: 10978226).

The variants' classification is based on the classification criteria set by the ACMG/AMP (PMID: 25741868) and the updated ClinGen gene-specific guidelines.

Notes:

Every molecular test has an internal 0,5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.

The variants reported in *PMS2* gene are detected with coverage >25%. The method used cannot detect low-level mosaicism (with coverage <25%).

The method in use achieves 99% sensitivity and specificity for single nucleotide variants and insertions and deletions <15bp. Sensitivity to detect genomic rearrangements larger than 15bp but smaller than a full exon may be reduced. Balanced genomic rearrangements and low-level mosaicism (<25%) cannot be detected.

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Details about non-pathogenic variants

Variants of uncertain significance (VUS) are reported when the *in-silico* analysis tools indicate a damaging effect on the protein function. Benign variants (Polymorphisms) are not reported, and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Genes Analyzed

Gene	Reference sequence	Gene	Reference sequence	Gene	Reference sequence	Gene	Reference sequence
APC	NM_000038	EPCAM*2	NM_002354	MSH3	NM_002439	RET	NM_020975
ATM*1,2	NM_000051	EXT1	NM_000127	MSH6*2	NM_000179	RNF43	NM_017763
AXIN2	NM_004655	EXT2	NM_000401	MTAP	NM_002451	SDHA	NM_004168
ATRX*1	NM_00489	FGFR1	NM_001174067	MUTYH*2	NM_001128425	SDHAF2	NM_017841
BAP1*1	NM_004656	FH	NM_000143	NBN*1	NM_002485	SDHB	NM_003000
BARD1*1,2	NM_000465	FLCN	NM_001458	NF1	NM_001042492	SDHC	NM_003001
BLM*1	NM_000057	GREM1	NM_013372	NF2	NM_181832	SDHD	NM_001276506
BMPR1A	NM_004329	H3-3A	NM_002107	NTHL1	NM_002528	SLX4	NM_032444
BRAF	NM_004333	HRAS	NM_176795	PALB2*1,2	NM_024675	SMAD4	NM_005359
BRCA1*1,2	NM_007294	IDH2	NM_002168	PDGFRA	NM_006206	SPINK1	NM_003122
BRCA2*1,2	NM_000059	KIF1B	NM_015074	PMS2	NM_000535	SQSTM1	NM_003900
BRIP1*1,2	NM_032043	KIT	NM_000222	POLD1	NM_001256849	STK11	NM_000455
CDH1	NM_004360	MAX	NM_145113	POLE	NM_006231	TMEM127	NM_017849
CDK4	NM_000075	MDH2	NM_005918	PRSS1	NM_002769	TP53*2	NM_000546
CDKN1C	NM_000076	MEN1	NM_000244	PTEN	NM_000314	TRIM28	NM_005762
CDKN2A	NM_001195132	MERTK	NM_006343	RAD50*1,2	NM_005732	TSC1	NM_000368
CHEK2*1,2	NM_007194	MET	NM_001127500	RAD51C*1,2	NM_058216	TSC2	NM_000548
CTR9	NM_014633	MLH1*2	NM_000249	RAD51D*1,2	NM_002878	VHL	NM_000551
EGLN1	NM_022051	MML2	NM_003482	RB1	NM_000321	WT1	NM_024476
EGLN2	NM_080732	MRE11A*1	NM_005591	RECQL4*1	NM_004260	XRCC2*1,2	NM_005431
EPAS1	NM_001430	MSH2*2	NM_000251	REST	NM_005612		

*1 Genes of the homologous recombination (HR) complex

*2 Unless otherwise noted analysis of large rearrangement was performed on the following genes: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM (Exons 8, 9), MLH1, MSH2, MSH6, MUTYH, PALB2, RAD50 (Exons 1, 2, 4, 10, 14, 21, 23 and 25), RAD51C, RAD51D and TP53.*

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Family tree

Note: **The information shown on the family tree has been provided by the patient and not by medical records.**

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